

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 1% and about 15% after 2 hours;
- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;

- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours.

2. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 4% and about 8% after 2 hours;
- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 4% and about 15% after 2 hours;

- (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- (d) in excess of about 80% after 24 hours.

3. The preparation of claim 1 or 2 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

4. The preparation of claim 1, 2 or 3 wherein the Diltiazem is in the form of Diltiazem HCl.

5. The preparation of claim 1, 2, 3 or 4 wherein the preparation is a diffusion controlled preparation.

6. The preparation of claim 1, 2, 3, 4 or 5 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

7. The preparation of claim 1, 2, 3, 4, 5 or 6 in capsule form.

8. The preparation of claim 1, 2, 3, 4, 5 or 6 in tablet form.

9. The preparation of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

10. The preparation of claim 9 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

11. The preparation of claim 10 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

12. The preparation of claim 9, 10 or 11 wherein the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer such as Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester) which hydrates the preparation.

13. The preparation of claim 9 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer such as Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester) which hydrates the preparation.

14. The preparation of claim 9, 10, 11, 12 or 13 wherein the membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.

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15. The preparation of claim 14 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

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16. The preparation of claim 10 or 11 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises Eudragit RS, Eudragit RL and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

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17. The preparation of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

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18. The preparation of claim 17 wherein the dissolution agent is an organic acid such as adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and the like which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

19. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 1 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

20. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

21. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 3 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.
28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

37. The preparation of claim 1, 2, 3, 4, 7, 8, 9, 11, 12, 13 or 14 wherein the preparation contains 120 mg of Diltiazem.

38. The preparation of claim 1, 2, 3, 4, 7, 8, 9, 11, 12, 13 or 14 wherein the preparation contains 180 mg of Diltiazem.

39. The preparation of claim 1, 2, 3, 4, 7, 8, 9, 11, 12, 13, or 14 wherein the preparation contains 240 mg of Diltiazem.

40. The preparation of claim 1, 2, 3, 4, 7, 8, 9, 11, 12, 13, or 14 wherein the preparation contains 300 mg of Diltiazem.

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41. The preparation of claim 1, 2, 3, 4, 7, 8, 9, 11, 12, 13, or 14 wherein the preparation contains 360 mg of Diltiazem.

42. The preparation of claim 1, 2, 3, 4, 7, 8, 9, 11, 12, 13, or 14 wherein the preparation contains 420 mg of Diltiazem.

43. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 37, 38, 39, 40, 41 or 42 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

44. The preparation of claim 9, 10, 11, 12, 13, 14, 15 or 16 wherein the wetting agent is selected from:

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sugars;

saccharose, mannitol, sorbitol;

lecithins;

$C_{12}$  to  $C_{20}$  fatty acid esters of saccarose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as sucrose stearate marketed under the trade name of Crodesta;

xylose esters or xylites;

polyoxyethylene glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France)

Metal salts such as NaCl or sodium lauryl sulphate.

*Sig B*

45. The preparation of claim 9 wherein the wetting agent is in association with the diltiazem in the bead and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester such as Eudragit NE30D enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

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46. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 44 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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47. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 45 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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48. The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 in which the core and membrane comprise:

		% W/W
✓ (a)	Diltiazem hydrochloride	69 - 73
✓ (b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
✓ (c)	Povidone K30	1 - 2
✓ (d)	Sucrose stearate (crodesta F150)	7 - 8
✓ (e)	Magnesium stearate NF	0.5 - 2.5
✓ (f)	Talc USP	0.5 - 5.0
✓ (g)	Titanium dioxide (USP)	0.15 - 0.3
✓ (h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
✓ (i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
✓ (k)	Eudragit NE30 D (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

49. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

50. The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (such as Eudragit NE30D), together with suitable adjuvants.

51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 50 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

52. The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (such as Eudragit NE30D), together with suitable adjuvants.

53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 52 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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54. The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

55. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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56. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core

containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (such as Eudragit NE30D), together with suitable adjuvants.

57. The preparation of claim 56 wherein the microgranules are in capsule form.

58. The preparation of claim 56 wherein the microgranules are in tablet form.

59. The preparation of claim 56, 57 or 58 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid

methyl ester (such as Eudragit NE30D), together with suitable adjuvants.

60. The preparation of claim 56, 57 or 58 wherein the core and membrane comprise:

	% W/W
(a) Diltiazem hydrochloride	69 - 73
(b) Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c) Povidone K30	1 - 2
(d) Sucrose stearate (crodesta F150)	7 - 8
(e) Magnesium stearate NF	0.5 - 2.5
(f) Talc USP	0.5 - 5.0
(g) Titanium dioxide (USP)	0.15 - 0.3
(h) Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i) Polysorbate 80 (tween)	0.01 - 0.025
(j) Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k) Eudragit NE30 D (dry of 30%)	7 - 11
Purified water USP	0 (used for mixing).

61. The preparation of claim 56, 58, 59 or 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

62. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56, 57, 58, 59, 60 and 61 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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